Supporting Information

Synthesis of chiral tetrahydroisoquinoline and C₂-symmetric bistetrahydroisoquinoline ligands and their application in the enantioselective Henry reaction

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Table 1: Chemical shifts of proton at C1 of THIQs and C₂-BIQs before and after N-methylation

Appendix: ¹H NMR and ¹³C NMR of N-Methylated THIQs 7a-h, 8 and C₂-BIQ 10b-c

¹H NMR, ¹³C NMR experimental data and HPLC spectra of β-nitroalcohols 13a-q

Table 1: Chemical shifts of protons at C1 of THIQs and C₂-BIQs before and after N-methylation

<table>
<thead>
<tr>
<th>R³</th>
<th>Before N-methylation</th>
<th>After N-methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>5.25 (s, 1H) (4a)</td>
<td>4.89 (s, 1H) (7a)</td>
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<tr>
<td>o-OMe-Ph</td>
<td>5.63 (s, 1H) (4b)</td>
<td>5.35 (s, 1H) (7b)</td>
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<tr>
<td>o-NH₂-Ph</td>
<td>6.19 (s, 1H) (4c)</td>
<td>5.59 (s, 1H) (7e)</td>
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<td>2-naphth</td>
<td>5.39 (s, 1H) (4d)</td>
<td>5.02 (s, 1H) (7d)</td>
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<td>n-Pr</td>
<td>3.43 (t, J=9 Hz, 1H) (4e)</td>
<td>3.54-3.66 (m, 3H) (7e)</td>
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<tr>
<td>i-Pr</td>
<td>3.43 (d, J=8.4 Hz, 1H) (4f)</td>
<td>3.14 (d, J=9.3 Hz, 1H) (7f)</td>
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<td>t-Bu</td>
<td>3.69 (s, 1H) (4g)</td>
<td>3.39 (s, 1H) (7g)</td>
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<tr>
<td>Cy</td>
<td>3.40 (d, J= 9.3 Hz, 1H) (4h)</td>
<td>3.13 (d, J= 9Hz, 1H) (7h)</td>
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<tr>
<td>X = 3,5-C₆H₄, R = H</td>
<td>5.17 (s, 2H) (5c)</td>
<td>4.87 (s, 2H) (10c)</td>
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<tr>
<td>X = -CH₂-, R = OMe</td>
<td>4.24 (t, J=7.2 Hz, 2H) (5b)</td>
<td>3.98 (t, J= 7.8 Hz, 2H) (10b)</td>
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</tbody>
</table>

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Appendix: $^1$H NMR and $^{13}$C NMR of $N$-Methylated THIQs 7a-h, 8 and $C_2$-BIQ 10b-c
Chiral amines
1H NMR NMe2 DMSO
400 030614
Chiral amines
1H NMR amino alcohol Cl-t-Bu N-Me
036614
Chiral amines
1H NMR-Ph-NH full methylation
166 090513

Chiral amines
13C THIQ-CH2OH-N-NH
$^1$H NMR and HPLC spectra of nitroaldol adduct 13a-q

**(S)-1-Phenyl-2-nitroethanol 13a**
The crude mixture from the reaction of benzaldehyde 11a and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13a as an oil in 82% yield. $^1$H NMR δ: 2.76 (br s, 1H), 4.39-4.56 (m, 2H), 5.37 (dd, $J= 9.3, 9.6$ Hz, 1H), 7.34-7.40 (m, 5H); $^{13}$C NMR δ: 71.0, 81.3, 126.0, 129.0, 129.1, 138.2. The ee of 80% was determined by HPLC using Chiralcel OD-H column: hexane: $i$-PrOH = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (minor) = 16.8 min for (R), $t_2$ (major) = 20.1 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[1]

**(S)-1-(4-nitrophenyl)-2-nitroethanol 13b**
The crude mixture from the reaction of 4-nitrobenzaldehyde 11b and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 3: 7 v/v) to obtain β-nitroalcohol product 13b as yellow solid in 91% yield. $^1$H NMR δ: 3.28 (br s, 1H), 4.47-4.66 (m, 2H), 5.48-5.56 (m, 1H), 7.63 (d, $J= 8.7$ Hz, 2H), 8.27 (d, $J= 8.7$ Hz, 2H). $^{13}$C NMR δ: 70.0, 80.6, 124.1, 127.0, 1455.4, 148.0. The ee of 54% was determined by HPLC (Chiralcel OD-H column): hexane: $i$-PrOH = 85:15, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$ (minor) = 16.7 min for (R), $t_2$ (major) = 20.9 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[1]
(S)-1-(4-chlorophenyl)-2-nitroethanol 13c
The crude mixture from the reaction of 4-chlorobenzaldehyde 11c and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13c as an oil in 88% yield. $^1$H NMR δ: 2.89 (br s, 1H), 4.47-4.62 (m, 2H), 5.44-5.47 (m, 1H), 7.34-7.40 (m, 4H). $^{13}$C NMR δ: 70.3, 80.1, 127.3, 129.3, 134.9, 136.5. The ee of 77% was determined by HPLC (Chiralcel OD-H column): hexane: $i$-PrOH = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$ (minor) = 12.8 min for (R), $t_2$ (major) =16.1 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[2]
(S)-1-(3-chlorophenyl)-2-nitroethanol 13d
The crude mixture from the reaction of 3-chlorobenzaldehyde 11d and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1:5 v/v) to obtain β-nitroalcohol product 13d as an oil in 80% yield. $^1$H NMR δ: 2.96 (br, s, 1H), 4.49-4.63 (m, 2H), 5.37-5.44 (m, 1H), 7.26-7.73 (4H, m). $^{13}$C NMR δ: 70.3, 81.0, 124.0, 126.2, 129.1, 130.3, 135.0, 140.0. The ee of 71% was determined by HPLC (Chiralcel OD-H column): hexane: IPA = 90:10, flow rate = 0.1 ml/min, wavelength = 215 nm, t₁ (minor) = 12.4 min for (R), t₂ (major) = 15.2 min for (S). Absolute stereochemistry was assigned by comparison of t₁ and t₂ with literature values.$^{[2]}$

(S)-1-(2-bromophenyl)-2-nitroethanol 13e
The crude mixture from the reaction of 2-bromobenzaldehyde 11e and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1:5 v/v) to obtain β-nitroalcohol product 13e as an oil in 96% yield. $^1$H NMR δ: 3.09 (s, 1H), 4.40-4.71 (m, 2H), 5.78-5.80 (m, 1H), 7.20-7.25 (m, 2H), 7.61-7.68 (m, 2H). $^{13}$C NMR δ: 70.3, 80.9, 120.4, 128.0, 130.0, 132.5, 137.3. The ee of 76% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t₁ (minor) = 8.7 min for (R), t₂ (major) = 9.4 min for (S). Absolute stereochemistry was assigned by comparison of t₁ and t₂ with literature values.$^{[2-3]}$
(S)-1-(3-bromophenyl)-2-nitroethanol 13f

The crude mixture from the reaction of 2-bromobenzaldehyde 11f and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13f as an oil in 79% yield. \(^1\)H NMR δ: 3.02 (s, 1H), 4.40-4.71 (m, 2H), 5.75-5.82 (m, 1H), 7.20-7.25 (m, 2H), 7.61-7.68 (m, 2H). \(^1^3\)C NMR δ: 70.2, 80.8, 123.1, 124.5, 129.0, 131.0, 133.1, 140.5. The ee of 74% was determined by HPLC (Chiralcel OD-H column): hexane: \(i\)-PrOH = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, \(t_1\) (minor) = 13.9 min for (R), \(t_2\) (major) = 17.9 min for (S). Absolute stereochemistry was assigned by comparison of \(t_1\) and \(t_2\) with literature values.\(^{[4]}\)
(S)-1-(4-bromophenyl)-2-nitroethanol 13g
The crude mixture from the reaction of 4-bromobenzaldehyde 11g and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1:5 v/v) to obtain β-nitroalcohol product 13g as an oil in 95% yield. $^1$H NMR δ: 2.96 (s, 1H), 4.40-4.54 (m, 2H), 5.36-5.39 (m, 1H), 7.19-7.23 (m, 2H), 7.45-7.48 (m, 2H). $^{13}$C NMR δ: 70.3, 80.9, 123.0, 127.6, 132.2, 137.1. The ee of 80% was determined by HPLC (Chiralcel OD-H column): hexane: $i$-PrOH = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (minor) = 13.5 min for (R), $t_2$ (major) = 17.6 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[5]

(S)-1-(2-fluorophenyl)-2-nitroethanol 13h
The crude mixture from the reaction of 4-florobenzaldehyde 11h and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1:7 v/v) to obtain β-nitroalcohol product 13h as an oil in 94% yield. $^1$H NMR δ: 2.92 (s, 1H), 4.43-4.60 (m, 2H), 5.69 (d, $J$=7.5 Hz, 1H), 7.02-7.17 (m, 2H), 7.32-7.50 (m, 2H). $^{13}$C NMR δ: 65.4, 79.8, 115.6, 124.8, 125.3, 127.7. The ee of 78% was determined by HPLC (Chiralpak AD-H column): hexane: $i$-PrOH = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (major) = 14.3 min for (S), $t_2$ (minor) = 15.2 min for (R). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[3]
(S)-1-(4-fluorophenyl)-2-nitroethanol 13i
The crude mixture from the reaction of 4-florobenzaldehyde 11i and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 7 v/v) to obtain β-nitroalcohol product 13i as an oil in 67% yield. $^1$H NMR $\delta$: 2.89 (s, 1H), 4.46-4.63 (m, 2H), 5.47 (d, $J$=7.5 Hz, 1H), 7.07-7.13 (m, 2H), 7.37-7.42 (m, 2H). $^{13}$C NMR $\delta$: 70.3, 81.2, 115.9, 116.1, 127.7, 127.8. The $ee$ of 78% was determined by HPLC (Chiralcel OD-H column): hexane: $i$-PrOH = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (major) = 14.8 min for (S), $t_2$ (minor) = 17.6 min for (R). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[6]
(S)-1-(4-methylphenyl)-2-nitroethanol 13j
The crude mixture from the reaction of 4-methylbenzaldehyde 11j and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 8 v/v) to obtain β-nitroalcohol product 13j as an oil in 83% yield. $^1$H NMR δ: 2.36 (s, 3H), 2.48 (s, 1H), 4.46-4.64 (m, 2H), 5.40-5.46 (m, 1H), 7.26-7.30 (m, 4H). $^{13}$C NMR δ: 21.2, 70.9, 81.3, 125.9, 129.7, 135.2, 139.0. The ee of 74% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ (minor) = 27.7 min for (R), $t_2$ (major) = 35.9 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.$^{[2\text{-}3]}$

(S)-1-(3-methylphenyl)-2-nitroethanol 13k
The crude mixture from the reaction of 3-methylbenzaldehyde 11k and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13k as an oil in 61% yield. $^1$H NMR δ: 2.38 (s, 3H), 2.81 (s, 1H), 4.50-4.65 (m, 2H), 5.37-5.45 (m, 1H), 7.23-7.32 (m, 4H). $^{13}$C NMR δ: 21.4, 71.1, 81.8, 123.0, 126.6, 128.9, 129.7, 138.0, 138.9. The ee of 71% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ (minor) = 23.3 min for (R), $t_2$ (major) = 26.9 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.$^{[2]}$
(S)-1-(2-methylphenyl)-2-nitroethanol 13l
The crude mixture from the reaction of 2-methylbenzaldehyde 11I and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1:5 v/v) to obtain β-nitroalcohol product 13l as an oil in 96% yield. $^1$H NMR δ: 2.40 (s, 3H), 2.72 (d, $J = 3.6$Hz, 1H), 4.42-4.60 (m, 2H), 5.67-5.72 (m, 1H), 7.25-7.31 (m, 3H), 7.51-7.56 (m, 1H). $^{13}$C NMR δ: 18.9, 6.80, 80.2, 125.6, 126.8, 130.9, 134.4 and 136.2. The ee of 78% was determined by HPLC (Chiralcel OD-H column): hexane: $i$-PrOH = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ (minor) = 21.9 min for (R), $t_2$ (major) = 33.7 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[1]
(S)-1-(biphenyl-4-yl)-2-nitroethanol 13m
The crude mixture from the reaction of 4-phenyllbenzaldehyde 11m and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13m as an oil in 93% yield. 
$^1$H NMR δ: 2.88 (d, $J$= 3.3Hz, 1H), 4.36-4.69 (m, 2H), 5.52 (d, $J$= 9.3Hz, 1H), 7.34-7.64 (m, 9H). 
$^{13}$C NMR δ: 70.8, 81.2, 126.4, 127.1, 127.7, 127.8, 128.9, 137.0, 140.3, 142.0. The ee of 68% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (minor) = 19.3 min for (R), $t_2$ (major) = 23.4 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.$^{[1]}$

(S)-1-(3-methoxyphenyl)-2-nitroethanol 13n
The crude mixture from the reaction of 3-methoxybenzaldehyde 11n and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13n as an oil in 80% yield. 
$^1$H NMR δ: 2.97 (br, s, 1H), 3.19 (s, 3H), 4.72-4.84 (m, 2H), 5.42-5.48 (m, 1H), 6.88-6.97 (m, 3H), 7.28-7.57 (m, 1H). 
$^{13}$C NMR δ: 55.3, 70.9, 81.2, 111.5, 114.4, 118.1, 130.1, 139.8, 160.1. The ee of 64% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ (minor) = 45.6 min for (R), $t_2$ (major) = 58.7 min for (S). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.$^{[2]}$
The crude mixture from the reaction of 2-naphthaldehyde \(1_{10}\) and nitromethane \(1_{2}\) was purified by flash chromatography (EtOAc: hexane, 1: 4 v/v) to obtain β-nitroalcohol product \(1_{3_{0}}\) as an oil in 93% yield. \(^1^H\) NMR δ: 3.04 (br, s, 1H), 4.54 - 4.82 (m, 2H), 5.61 (d, \(J=6.9\)Hz, 1H), 7.26-7.54 (m, 3H), 7.84-7.88 (m, 4H). \(^1^C\) NMR δ: 71.2, 81.2, 123.2, 125.3, 126.7, 126.7, 127.8, 128.1, 129.0, 133.2, 133.4, 135.4. The ee of 78% was determined by HPLC (Chiralcel OD-H column): hexane: \(i\)-PrOH = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, \(t_{1}\) (minor) = 34.7 min for (R), \(t_{2}\) (major) = 50.8 min for (S). Absolute stereochemistry was assigned by comparison of \(t_{1}\) and \(t_{2}\) with literature values.\[^{[1]}\]
**(S, E)-1-Nitro-4-phenyl-3-buten-2-ol 13p**

The crude mixture from the reaction of 2-naphthaldehyde 11p and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13p as an oil in 76% yield. $^1$H NMR δ: 2.68 (br s, 1H), 4.51 - 4.61 (m, 2H), 5.02 - 5.08 (m, 1H), 6.15 (dd, $J = 6.3$, 15.9 Hz, 1H), 6.79 (d, $J = 15$ Hz, 1H), 7.30 - 7.46 (m, 5H). $^{13}$C NMR δ: 69.6, 79.9, 124.9, 126.7, 128.6, 128.8, 133.7, 135.5. The ee of 61% was determined by HPLC (Chiralcel OD-H column): hexane: i-PrOH = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ (major) = 54.0 min for (S), $t_2$ (minor) = 61.3 min for (R). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[3]

**(R)-1-(2-Fural)-2-nitroethanol 13q**

The crude mixture from the reaction of 2-furaldehyde 11q and nitromethane 12 was purified by flash chromatography (EtOAc: hexane, 1: 5 v/v) to obtain β-nitroalcohol product 13q as an oil in 76% yield. 1H NMR (300 MHz, CDCl3, δ ppm): 2.90 (1H, br, s, OH), 4.63 - 4.84 (2H, m, CH2NO2), 5.40 - 5.50 (1H, m, CHOH), 6.38 - 6.40 (2H, m, ArH), 7.40 - 7.42 (1H, m, ArH); 13C NMR (75.6 MHz, CDCl3, δ ppm): 64.9, 78.4, 108.2, 100.7, 143.2 and 150.7. The ee of 77% was determined by HPLC. HPLC (Chiralcel OJ-H column): n-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$ (minor) = 23.1 min for (S), $t_2$ (major) = 28.5 min for (R). Absolute stereochemistry was assigned by comparison of $t_1$ and $t_2$ with literature values.[5, 7]